General

Guideline Title

Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline.

Bibliographic Source(s)

Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA, Wass JA, Endocrine Society. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011 Feb;96(2):273-88. [137 references] PubMed

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

Definitions for the quality of the evidence (+OOO, ++OO, +++O, and ++++); the strength of the recommendation (1 or 2); and the difference between a "recommendation" and a "suggestion" are provided at the end of the "Major Recommendations" field.

Diagnosis of Hyperprolactinemia

To establish the diagnosis of hyperprolactinemia, the Task Force recommends a single measurement of serum prolactin; a level above the upper limit of normal confirms the diagnosis as long as the serum sample was obtained without excessive venipuncture stress. The Task Force recommends against dynamic testing of prolactin secretion for the diagnosis of hyperprolactinemia (1|++++).

In patients with asymptomatic hyperprolactinemia, the Task Force suggests assessing for macroprolactin (2|++OO).

When there is a discrepancy between a very large pituitary tumor and a mildly elevated prolactin level, the Task Force recommends serial dilution of serum samples to eliminate an artifact that can occur with some immunoradiometric assays leading to a falsely low prolactin value ("hook effect") (1|++++).

Causes of Hyperprolactinemia

The Task Force recommends excluding medication use, renal failure, hypothyroidism, and parasellar tumors in patients with symptomatic nonphysiological hyperprolactinemia (1|++++).

Management of Drug-Induced Hyperprolactinemia

In a symptomatic patient with suspected drug-induced hyperprolactinemia, the Task Force suggests discontinuation of the medication for 3 days (d) or substitution of an alternative drug, followed by remeasurement of serum prolactin (2|++OO). Discontinuation or substitution of an antipsychotic agent should not be undertaken without consulting the patient's physician. If the drug cannot be discontinued and the onset of the hyperprolactinemia does not coincide with therapy initiation, the Task Force recommends obtaining a pituitary magnetic resonance image (MRI) to differentiate between medication-induced hyperprolactinemia and symptomatic hyperprolactinemia due to a pituitary or hypothalamic mass (1|+OOO).

The Task Force suggests that clinicians not treat patients with asymptomatic medication-induced hyperprolactinemia (2|++OO). The Task Force suggests use of estrogen or testosterone in patients with long-term hypogonadism (hypogonadal symptoms or low bone mass) related to medication-induced hyperprolactinemia (2|+OOO).

The Task Force suggests that the first step in treatment of medication-induced hyperprolactinemia is to stop the drug if this is clinically feasible. If this is not possible, a drug with a similar action that does not cause hyperprolactinemia should be substituted, and if this is not feasible the Task Force suggests considering the cautious administration of a dopamine agonist in consultation with the patient's physician (2|+OOO).

Management of Prolactinoma

The Task Force recommends dopamine agonist therapy to lower prolactin levels, decrease tumor size, and restore gonadal function for patients harboring symptomatic prolactin-secreting microadenomas or macroadenomas (1|++++). The Task Force recommends using cabergoline in preference to other dopamine agonists because it has higher efficacy in normalizing prolactin levels, as well as a higher frequency of pituitary tumor shrinkage (1|++++).

The Task Force suggests that clinicians not treat asymptomatic patients harboring microprolactinomas with dopamine agonists (2|+OOO). The Task Force suggests treatment with a dopamine agonist or oral contraceptives in patients with a microadenoma who have amenhorrhea (2|+OOO).

The Task Force suggests that with careful clinical and biochemical follow-up, therapy may be tapered and perhaps discontinued in patients who have been treated with dopamine agonists for at least 2 years, who no longer have elevated serum prolactin, and who have no visible tumor remnant on MRI (2|+OOO).

Resistant and Malignant Prolactinoma

For symptomatic patients who do not achieve normal prolactin levels or show significant reduction in tumor size on standard doses of a dopamine agonist (resistant prolactinomas), the Task Force recommends that the dose be increased to maximal tolerable doses before referring the patient for surgery (1|++++).

The Task Force recommends that patients resistant to bromocriptine be switched to cabergoline (1|++++).

The Task Force suggests that clinicians offer transsphenoidal surgery to symptomatic patients with prolactinomas who cannot tolerate high doses of cabergoline or who are not responsive to dopamine agonist therapy. For patients who are intolerant of oral bromocriptine, intravaginal administration may be attempted. For patients who fail surgical treatment or who harbor aggressive or malignant prolactinomas, the Task Force suggests radiation therapy (2|+OOO).

In patients with malignant prolactinomas, the Task Force suggests temozolomide therapy (2|+OOO).

Management of Prolactinoma During Pregnancy

The Task Force recommends that women with prolactinomas be instructed to discontinue dopamine agonist therapy as soon as they discover that they are pregnant (1|++OO).

In selected patients with macroadenomas who become pregnant on dopaminergic therapy and who have not had prior surgical or radiation therapy, it may be prudent to continue dopaminergic therapy throughout the pregnancy, especially if the tumor is invasive or is abutting the optic chiasm (1|+OOO).

In pregnant patients with prolactinomas, the Task Force recommends against performing serum prolactin measurements during pregnancy (1|++++).

The Task Force recommends against the use of routine pituitary MRI during pregnancy in patients with microadenomas or intrasellar macroadenomas unless there is clinical evidence for tumor growth such as visual field compromise (1|++OO).

The Task Force recommends that women with macroprolactinomas who do not experience pituitary tumor shrinkage during dopamine agonist

therapy or who cannot tolerate bromocriptine or cabergoline be counseled regarding the potential benefits of surgical resection before attempting pregnancy (1|++OO).

The Task Force recommends formal visual field assessment followed by MRI without gadolinium in pregnant women with prolactinomas who experience severe headaches and/or visual field changes (1|++OO).

The Task Force recommends bromocriptine therapy in patients who experience symptomatic growth of a prolactinoma during pregnancy (1|++OO).

Definitions:

Quality of Evidence

+OOO Denotes very low quality evidence

++OO Denotes low quality evidence

+++O Denotes moderate quality evidence

++++ Denotes high quality evidence

Strength of Recommendation

1 - Indicates a strong recommendation and is associated with the phrase "The Task Force recommends."

2 - Denotes a weak recommendation and is associated with the phrase "The Task Force suggests."

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Hyperprolactinemia, including:

- Drug-induced hyperprolactinemia
- Prolactinoma
- Resistant and malignant prolactinoma
- Prolactinoma during pregnancy

Guideline Category

Diagnosis

Evaluation

Management

Treatment

Clinical Specialty

Endocrinology

Neurology

Obstetrics and Gynecology

Psychiatry

Intended Users

Advanced Practice Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To formulate practice guidelines for the diagnosis and treatment of hyperprolactinemia

Target Population

Patients with hyperprolactinemia, including pregnant women with prolactinomas

Interventions and Practices Considered

Diagnosis/Evaluation

1. Measurement of serum prolactin levels
2. Assessment for macroprolactin in asymptomatic patients
3. Serial dilution of serum samples to eliminate artifacts
4. Excluding causes of hyperprolactinemia (e.g., medication use, renal failure, hypothyroidism, pituitary tumors)

Management/Treatment

1. Management of drug-induced hyperprolactinemia
    - Discontinuation of medication or substitution of alternative medication
    - Use of estrogen or testosterone in patients with long-term hypogonadism
    - Cautious administration of a dopamine agonist in consultation with the patient's physician
2. Management of prolactinoma
    - Dopamine agonist therapy, with preferential use of cabergoline
    - Oral contraceptives in patients with amenorrhea and microadenoma
    - Tapering and discontinuation of therapy
3. Management of resistant and malignant prolactinoma
    - Increasing dose of dopamine agonist therapy
    - Switching from bromocriptine to cabergoline
    - Transsphenoidal surgery
    - Transvaginal administration of bromocriptine
    - Radiation therapy
    - Temozolomide therapy
4. Management of prolactinoma during pregnancy
    - Discontinuation of dopamine agonist therapy
    - Refraining from measuring serum prolactin in pregnant patients with prolactinomas
    - Refraining from routine pituitary magnetic resonance imaging (MRI)
    - Counseling regarding the potential benefits of surgical resection before attempting pregnancy
    - Formal visual field assessment followed by MRI without gadolinium in pregnant women with prolactinomas experiencing severe

headaches and/or visual field changes
- Bromocriptine therapy for symptomatic growth of prolactinoma during pregnancy

Major Outcomes Considered

- Symptom improvement (including tumor size, visual field, amenorrhea, infertility, sexual function, galactorrhea)
- Prolactin levels

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

A systematic review of the literature was commissioned by The Endocrine Society to evaluate the treatment effects of dopamine agonists in patients with hyperprolactinemia (see the "Availability of Companion Documents" field).

Data Sources: MEDLINE, EMBASE, Cochrane CENTRAL, Web of Science and Scopus were searched through September 2009. Review of bibliography of included articles and contact with experts further identified candidate studies. See the systematic review (see the "Availability of Companion Documents" field) for specific search terms.

Study Selection: Pairs of reviewers — working independently — reviewed abstracts and titles and then full text of articles.

Number of Source Documents

204 studies fulfilled inclusion criteria: 41 were comparative studies, 10 were non-interventional/natural history studies, and 157 were studies involving multiple treatment modalities without control group.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Quality of Evidence

+OOO Denotes very low quality evidence

++OO Denotes low quality evidence

+++O Denotes moderate quality evidence

++++ Denotes high quality evidence

Methods Used to Analyze the Evidence

Meta-Analysis of Randomized Controlled Trials

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

A systematic review of the literature was commissioned by The Endocrine Society to evaluate the treatment effects of dopamine agonists in patients with hyperprolactinemia (see the "Availability of Companion Documents" field).

Study Selection: Pairs of reviewers — working independently — reviewed abstracts and titles and then full text of articles.

Data Extraction: Data extraction was done in duplicate until chance-adjusted interobserver agreement (kappa) > 90%. Reviewers determined the methodological quality of studies and collected descriptive, quality and outcome data (prolactin level, tumor size, visual field defects, infertility, sexual dysfunction, amenorrhea/oligomenorrhea).

Data Synthesis: From each study, the relative risk (or risk ratio, [RR]) and 95% confidence interval (CI) for dichotomous outcomes and weighted difference in means (WMD) and 95% CI for continuous outcome were estimated. Data were pooled using the random effects model and heterogeneity assessed using the I squared statistic. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to evaluate the quality of evidence.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The Task Force consisted of Endocrine Society-appointed experts, a methodologist, and a medical writer.

One group meeting, several conference calls, and e-mail communications enabled consensus.

Rating Scheme for the Strength of the Recommendations

Strength of Recommendation

1 - Indicates a strong recommendation and is associated with the phrase "The Task Force recommends."

2 - Denotes a weak recommendation and is associated with the phrase "The Task Force suggests."

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Committees and members of The Endocrine Society, The European Society of Endocrinology, and The Pituitary Society reviewed and

commented on preliminary drafts of these guidelines.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is specifically stated for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Accurate diagnosis and appropriate treatment of hyperprolactinemia

Potential Harms

- Some studies suggest that dopamine agonist therapy will normalize prolactin levels in only up to 75% of patients on anti-psychotics but may lead to exacerbation of the underlying psychosis.
- Although high doses of cabergoline may be necessary to overcome resistance, caution must be exhibited with protracted use of high-dose cabergoline because of the potential risk of cardiac valvular regurgitation. Patients with Parkinson's disease receiving at least 3 mg of cabergoline daily are at risk for moderate to severe cardiac valve regurgitation. In contrast, six of seven studies analyzing cardiac valves in over 500 patients with prolactinomas receiving standard doses of cabergoline have shown no evidence of clinically significant valvular disease. The one study that did report a 57% incidence of tricuspid regurgitation in patients treated with cabergoline also noted significant tricuspid regurgitation in the control group.
- Side effects of surgery, which are less commonly encountered with experienced pituitary surgeons, include hypopituitarism, diabetes insipidus, cerebrospinal fluid leak, and local infection.
- Radiation therapy is associated with side effects including hypopituitarism and, rarely, cranial nerve damage or second tumor formation.
- Quinagolide has a poor safety profile in the relatively small number of pregnancies that have been reported, and it should not be prescribed to women desirous of becoming pregnant.

Qualifying Statements

Qualifying Statements

- Clinical Practice Guidelines are developed to be of assistance to endocrinologists and other health care professionals by providing guidance and recommendations for particular areas of practice. The Guidelines should not be considered inclusive of all proper approaches or methods, or exclusive of others. The Guidelines cannot guarantee any specific outcome, nor do they establish a standard of care. The Guidelines are not intended to dictate the treatment of a particular patient. Treatment decisions must be made based on the independent judgment of health care providers and each patient's individual circumstances.
- The Endocrine Society makes no warranty, express or implied, regarding the Guidelines and specifically excludes any warranties of merchantability and fitness for a particular use or purpose. The Society shall not be liable for direct, indirect, special, incidental, or consequential damages related to the use of the information contained herein.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Patient Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

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Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2011 Feb

Guideline Developer(s)

The Endocrine Society - Professional Association

Source(s) of Funding

The Endocrine Society

Guideline Committee

Diagnosis and Treatment of Hyperprolactinemia Task Force

Composition of Group That Authored the Guideline

Task Force Members: Shlomo Melmed (*Chair*); Felipe F. Casanueva; Andrew R. Hoffman; David L. Kleinberg; Victor M. Montori; Janet A. Schlechte; John A. H. Wass

Financial Disclosures/Conflicts of Interest

Shlomo Melmed (chair)—Financial or Business/Organizational Interests: Novartis, Ipsen; Significant Financial Interest or Leadership Position: International Society of Endocrinology, The Pituitary Society.

Felipe F. Casanueva—Financial or Business/Organizational Interests: Pfizer, Novo Nordisk, Novartis; Significant Financial Interest or Leadership Position: International Society of Endocrinology, Pituitary Society.

Andrew R. Hoffman—Financial or Business/Organizational Interests: Merck Serono, LG Life Sciences, Teva, Novartis, Theratechnologies, Pfizer; Significant Financial Interest or Leadership Position: Ambrx, Inc., Human Growth Foundation.

David L. Kleinberg—Financial or Business/Organizational Interests: Novartis Pharmaceuticals, Eli Lilly, U .S. Department of Defense; Significant Financial Interest or Leadership Position: The Pituitary Society.

Victor M. Montori*—Financial or Business/Organizational Interests: Knowledge and Encounter Research Unit (Mayo Clinic); Significant Financial Interest or Leadership Position: none declared.

Janet A. Schlechte—Financial or Business/Organizational Interests: none declared; Significant Financial Interest or Leadership Position: none declared.

John A. H. Wass—Financial or Business/Organizational Interests: Pfizer, Novo Nordisk, Novartis, Ipsen, Merck Serono; Significant Financial Interest or Leadership Position: The Pituitary Society.

*Evidence-based reviews for this guideline were prepared under contract with The Endocrine Society.

Guideline Endorser(s)

European Society of Endocrinology - Medical Specialty Society

The Pituitary Society - Professional Association

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from The Endocrine Society Web site .

Print copies: Available from The Endocrine Society, Phone: (301) 941.0210; Email: Societyservices@endo-society.org.

Availability of Companion Documents

The following is available:

- Wang A, Mullan R, Lane M, Prasad C, Mwirigi N, Fernandez M, Bagatto A, Hazem A, Coto-Iglysias F, Carey J, Kovalaske M, Erwin P, Ghandhi G, Murad MH, Montori VM. Outcomes of treated and untreated hyperprolactinemia: a systematic review and meta-analysis. Rochester (MN): Mayo Clinic College of Medicine; 2011. 40 p.

Print copies: Available from The Endocrine Society, Phone: (301) 941.0210; Email: Societyservices@endo-society.org.

Patient Resources

The following are available:

- Patient guide to hyperprolactinemia diagnosis and treatment. The Hormone Foundation. 2011 Feb. 2 p. Electronic copies: Available from The Hormone Foundation Web site .
- Fact sheet: hyperprolactinemia diagnosis and treatment. The Hormone Foundation. 2010 Jan. 1 p. Electronic copies: Available in Portable Document Format (PDF) from The Hormone Foundation Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This NGC summary was completed by ECRI Institute on January 10, 2012. The information was verified by the guideline developer on February 3, 2012. This summary was updated by ECRI Institute on April 3, 2015 following the U.S. Food and Drug Administration advisory on Testosterone Products.

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